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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/384,959	08/27/99	SASISEKHARAN R	MIT-6747HC

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EXAMINER	
HUTSON, R	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 09/11/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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PTO-90C (Rev.11/00)
*U.S. GPO: 2000-475-249/45175

2 - Mail Copy

Office Action Summary	Application No.	Applicant(s)	
	09/384,959	SASISEKHARAN ET AL.	
	Examiner	Art Unit	
	Richard G Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 July 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-57* is/are pending in the application.

4a) Of the above claim(s) *1-29,32,35-45 and 50-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30,31,33,34,46 and 47* is/are rejected.

7)☒ Claim(s) *49* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Notice of References Cited	Application/Control No. 09/384,959	Applicant(s)/Patent Under Reexamination SASISEKHARAN ET AL.	
	Examiner Richard G Hutson	Art Unit 1652	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification	
	A	US-5,681,733	10-1997	Su et al.	435	232
	B	US-				
	C	US-				
	D	US-				
	E	US-				
	F	US-				
	G	US-				
	H	US-				
	I	US-				
	J	US-				
	K	US-				
	L	US-				
	M	US-				

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification	
	N						
	O						
	P						
	Q						
	R						
	S						
	T						

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

DETAILED ACTION

Claims 1-57 are at issue and are present for examination.

Applicant's election of Group III, Claims 30-34, 46-49 in Paper No. 13 is acknowledged. Applicants additionally elect the species of the methods involving heparinase II. It is acknowledged that applicants have not traversed the above restriction requirement. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-29, 32, 35-45 and 50-57 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claim Objections

Claims 30, 31, 33, 34 and 45-49 are objected to because of the following informalities: Claims 30, 31, 33, 34 and 45-49 depend on non-elected claims 1, 8 or 22. Claim 49 is further dependent on rejected claim 46.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 33, 34, 47 and 48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 33 (34 dependent on) and 47 (48 dependent on) are indefinite in the recitation "...a method of removing active heparin..." It is unclear what applicants intend to be encompassed by "active heparin". Is "active heparin" different than "heparin". It is this confusion that makes claims 33 and 34 indefinite.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 30, 33, 34, 46, 47 and 48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to methods of specifically cleaving a heparin-like glycosaminoglycan, comprising contacting a heparin-like glycosaminoglycan with the heparinase of claims 1 or 8, wherein said heparinase comprises a modified heparinase II having a modified product profile that is at least 10% different than a native product profile of a native heparinase II (claim 1) or wherein said heparinase comprises a modified heparinase II that can cleave a glycosaminoglycan substrate having a modified heparinase II k_{cat} value at least 10% different than a native heparinase II k_{cat} value. The specification fails to describe in any fashion the physical and/or chemical properties of the claimed class of substances and identifies only those modified heparinase II enzymes having the amino acid sequence of SEQ ID NO: 2 with either a specific

substitution at histidine 440 or cysteine 348, as members of the class of modified heparinases having the necessary functional properties. Moreover, the specification fails to describe any other representative species of modified heparinase II enzymes by any identifying characteristics or properties other than the functionality of having heparinase activity and a modified product profile that is at least 10% different than a native product profile of a native heparinase II or that has a modified heparinase II k_{cat} value at least 10% different than a native heparinase II k_{cat} value. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claims 30, 33, 34, 46, 47 and 48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for those methods of cleaving a heparin-like or heparan sulfate-like glycosaminoglycan comprising contacting said heparin-like or heparan sulfate-like glycosaminoglycan with a modified heparinase II comprising SEQ ID NO: 2 with a specific substitution at histidine 440 or cysteine 348, does not reasonably provide enablement for those methods of cleaving a heparin-like or heparan sulfate-like glycosaminoglycan comprising contacting said heparin-like or heparan sulfate-like glycosaminoglycan with any modified heparinase having a modified product profile or heparinase k_{cat} that is at least 10% different than the native heparinase II. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 30, 33, 34, 46, 47 and 48 are so broad as to encompass those methods of cleaving a heparin-like or heparan sulfate-like glycosaminoglycan comprising contacting said heparin-like or heparan sulfate-like glycosaminoglycan with any modified heparinase having a modified product profile or heparinase k_{cat} that is at least 10% different than the native heparinase II. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of modified heparinase II enzymes broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the claimed methods using those modified heparinase II enzymes having the amino acid sequence of SEQ ID NO: 2 with either a specific substitution at histidine 440 or cysteine 348.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the

desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any heparinase II, from any species, having any amino acid sequence and having a modified product profile or heparinase II k_{cat} that is at least 10% different than the native heparinase II, because the specification does not establish: (A) regions of the protein structure which may be modified without effecting heparinase II activity; (B) the general tolerance of heparinase II to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues of heparinase II with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including methods involving any number of amino acid modifications of any heparinase II wherein said modification results in having a 10% change in the product profile or heparinase k_{cat} relative to the native heparinase II. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of those modified heparinase II enzymes having the desired biological

characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 30, 31, 33, 46 and 47 are rejected under 35 U.S.C. 102(a) as being anticipated by Shriver et al. (Journal of Biological Chemistry 273(17): 10160-10167, April 1998).

Shriver et al. teach the role of histidine residues in enzymatic activity as probed by chemical modification and site-directed mutagenesis. Shriver specifically teach a modified heparinase II from *Flavobacterium heparinum* comprising a histidine 440 to alanine substitution and a method using said modified heparinase II to cleave heparin and heparan sulfate. Shriver et al. further teach that this modified heparinase II had less activity than recombinant heparinase II towards heparin. While they do not show that this is a result of at least a 10% difference in the kcat for heparin, it is believed that

this is an inherent property of this modified heparinase based on its decreased enzymatic activity towards heparin relative to the native heparinase II.

Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

It is acknowledged that the above rejection can be overcome by the filing of a declaration under CFR 1.131.

Claims 30, 33, 46 and 47 and are rejected under 35 U.S.C. 102(e) as being anticipated by Su et al. (U.S. Patent No: 5,681,733, filed 6/10/1994).

Su et al. teach the isolation and sequence of the genes encoding heparinase II and III from Flavobacterium heparinum as well as the expression of heparinase I, II and III. Su et al. further teach the properties of each of these three heparinases which involves determination of substrate specificity as well as k_{cat} (See Table 2). Since the claimed method is to a method of cleavage of a heparin or heparan sulfate-like glycosaminoglycans using a modified heparinase II that is described only by its functional attributes relative to the native heparinase II, the use of heparinases I and III in the taught cleavage methods anticipates claims 30, 33, 46 and 47.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 34 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Su et al. (U.S. Patent No: 5,681,733, filed 6/10/1994) as applied to Claims 30, 33, 46 and 47 above, and further in view of Langer et al. (U.S. Patent No. 4,373,023, issued 2/8/1983).

As discussed above, Su et al. teach the isolation and sequence of the genes encoding heparinase II and III from *Flavobacterium heparinum* as well as the expression of heparinase I, II and III. Su et al. further teach the properties of each of these three heparinases which involves determination of substrate specificity as well as k_{cat} (See Table 2). As discussed above, Su et al. anticipates the modified heparinase II enzymes of claims 1 and 8.

Langer et al. teach a process for neutralizing heparin from blood comprising treating the blood containing heparin extracorporeally with immobilized heparinase prior to being introduced into the patient. Langer et al. further teach that the heparinase which is that produced by Flavobacterium heparinum is immobilized on any of a number of supports such as Sepharose or polyacrylamide.

One of ordinary skill in the art at the time of invention would have been motivated to use the recombinantly produced heparinases such as heparinase I or III of Su et al. in the method of Langer et al. for cleaving heparin and removing said heparin from blood

extracorporeally by immobilizing heparinase to a solid support. The motivation for using the heparinases of Su et al. in the above methods is that because Su et al. have isolated the encoding genes for each of the heparinases, they can each be produced recombinantly. The many advantages of recombinant production of useful proteins are well known within the art. These advantages include the ability to produce much larger quantities of the protein, being able to produce the protein in more easily handled organisms, reducing the number of steps necessary for the purification of a protein and producing the protein in a purer form by using an organism that does not include naturally occurring contaminants of the protein. Thus claims 34 and 48 are made obvious by Su et al. and Langer et al.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapy Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Richard Hutson, Ph.D.
September 9, 2001

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP 1600

FORM PTO-1449(Modified)	ATTY. DOCKET NO.: M0656/7046	SERIAL NO.: 09/384, 959
LIST OF PATENTS AND PUBLICATIONS FOR APPLICANT'S INFORMATION DISCLOSURE STATEMENT	APPLICANT: Sasisekharan et al.	
	FILING DATE: August 27, 1999	GROUP: 1643

FOREIGN PATENT DOCUMENTS

		Country & Doc. No. (11)	Pub. Date (43)		Class	Sub Class	Translation Yes	Translation No
RH		W0 95 34635 A	12/21/95	IBEX Technologies				
RH		PCT/US99/19841	4/27/00	PCT Search Report				

OTHER ART
(Including Author, Title, Date, Pertinent Pages, Publication, Etc.)

RH			Shriver, Z.. et al., "Heparinase II from flavobacterium hepainum: Role of histidine residues in enzymatic activity as probed by chemical modification and site-directed mutagenesis," *Journal of Biological Chemistry*, Vol. 273, No 36, 1998, pp. 10160-10167
RH			Shriver, Z.. et al., "Heparinase II from flavobacterium hepainum: Role of cysteine in enzymatic activity as probed by chemical modification and site-directed mutagenesis," *Journal of Biological Chemistry*, Vol. 273, No 17, 1998, pp. 22904-22912

Richard Stubbs 8/28/01